
Epithelial mesenchymal transition and hedgehog signaling activation are associated with chemoresistance and invasion of hepatoma subpopulations.

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Public Summary:

Our previous studies showed that CD133, EpCAM, and aldehyde dehydrogenase (ALDH) are useful markers to identify cancer stem cells (CSCs) in hepatocellular carcinoma (HCC) tissues. The present study aims to evaluate chemosensitivity and invasion capability of HCC based on CSC marker profiles, and to explore the underlying molecular mechanisms.

Scientific Abstract:

BACKGROUND & AIMS: Our previous studies showed that CD133, EpCAM, and aldehyde dehydrogenase (ALDH) are useful markers to identify cancer stem cells (CSCs) in hepatocellular carcinoma (HCC) tissues. The present study aims to evaluate chemosensitivity and invasion capability of HCC based on CSC marker profiles, and to explore the underlying molecular mechanisms. **METHODS:** Hepatoma cell lines were separated into subpopulations according to CD133, EpCAM, and ALDH expression profiles. Epithelial mesenchymal transition (EMT) and hedgehog (Hh) signaling were examined to identify their links with chemoresistance and aggressive invasion. **RESULTS:** Well-differentiated cell lines were positive for CD133(+)/ALDH(high) and CD133(+)/EpCAM(+) at 1.5-15% and 2.3-8.3%; whereas, poorly-differentiated cells were almost all negative for these markers. FACS-enriched CD133(+)/ALDH(high) and CD133(+)/EpCAM(+) Hep3B and Huh-7 cells formed more spheroids in vitro. CD133(-)/ALDH(low) HLE cells were more resistant to cisplatin, doxorubicin or sorafenib than their positive counterparts. CD133(-)/EpCAM(-) Huh-7 cells or CD133(-)/ALDH(-) HLE cells exhibited a higher invasion rate than their positive counterparts. HLE and HLF cells acquired EMT in double negative subpopulations. Hh activity in Huh-7 CD133(-)/EpCAM(-) cells was higher than in their positive counterparts, and the inhibition of Hh activity by cyclopamine resulted in reduced cell proliferation. **CONCLUSIONS:** Well-differentiated CD133(+)/ALDH(high) or CD133(+)/EpCAM(+) cells appear to be a CSC/initiating subpopulation; whereas, in poorly-differentiated hepatoma cells, EMT and enhanced hedgehog signaling activity may be responsible for their chemoresistance and invasion. These findings underscore the significance of EMT and enhanced Hh signaling in liver cancer stem or initiating cells.

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